Practitioner's Docket No. U 013785-7 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Vidya Bhushan LOHRAY, et al.

For: NOVEL HETEROCYCLIC COMPOUNDS, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE IN THE TREATMENT OF DIABETES AND RELATED DISEASES

Box Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

Please amend the above identified application as follows:

IN THE SPECIFICATION:

Please amend the application as follows:

The first full paragraph on page 10 has been amended as follows:

--When R^1, R^2 and R^3 groups are attached to X, Y, and Z it is preferred that R^1, R^2, and R^3 are selected from hydrogen, halogen atom such as fluorine, chlorine, bromine,

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CERTIFICATE UNDER 37 1.10

I hereby certify that this paper is being deposited with the United States Postal Service on this date DECEMBER 26, 2001 in an envelope as "EXPRESS MAIL POST OFFICE TO ADDRESSEE" Mailing Label Number EV011019918US addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231

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or iodine; hydroxy, nitro; substituted or unsubstituted (C_1-C_{12})alkyl group, especially, linear or branched (C_1-C_6)alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, t-butyl and the like; cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like; cycloalkyloxy group such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and the like; aryl group such as phenyl or naphthyl, the aryl group may be substituted; aralkyl such as benzyl or phenethyl, the aralkyl group may be substituted; heteroaryl group such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, oxadiazolyl, tetrazolyl, benzopyranyl, benzofuranyl and the like, the heteroaryl group may be substituted; heterocyclyl groups such as aziridinyl, pyrrolidinyl, morpholinyl, piperidinyl and the like, the heterocyclyl group may be substituted; aryloxy such as phenoxy, naphthyloxy, the aryloxy group may be substituted; alkoxycarbonyl such as methoxycarbonyl or ethoxycarbonyl; aryloxycarbonyl group such as optionally substituted phenoxycarbonyl; arylamino group such as HNC_6H_5; amino group; amino(C_1-C_6)alkyl; hydroxy(C_1-C_6)alkyl; (C_1-C_6)alkoxy; thio(C_1-C_6)alkyl; (C_1-C_6)alkylthio; acyl group such as acetyl, propionyl or benzoyl, the acyl group may be substituted; acylamino groups such as $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_6H_5$, aralkoxycarbonylamino group such as $NHCOOCH_2C_6H_5$; alkoxycarbonylamino group such as $NHCOOC_2H_5$, $NHCOOCH_3$ and the like; carboxylic acid or its derivatives such as amides, like $CONH_2$, CONHMe, $CONMe_2$, CONHEt, $CONEt_2$, CONHPh and the like, the carboxylic acid derivatives may be substituted; acyloxy group such as OCOMe, OCOEt, OCOPh and the like which may optionally be substituted; sulfonic acid or its derivatives such as SO_2NH_2, SO_2NHMe, SO_2NMe_2, SO_2NHCF_3 and the like; the sulfonic acid derivatives may be substituted.--

The first full paragraph on page 28 has been amended as follows:

--The process described in the above embodiment is novel and unique since the heterocycle has been built in the final step of the process. In the present process no side products

are observed. The yields are high and no purification is required for any intermediate involved. The process described in the above embodiment does not involve any stringent conditions. This process works well for both small scale and large scale reactions. The process described in the above embodiment is preferably used for compounds of formula (I) wherein R^2 and R^3 together form a cyclic structure as defined earlier with Y, wherein Y represents C=C.--

The last full paragraph on page 32 has been amended as follows:

--The reaction of compound of the formula (XXIV) with a compound of formula (XXV) to yield a compound of the formula (XXVI) may be carried out neat or in presence of solvent such as xylene, toluene, dioxane, DMF, DMSO, halogenated hydrocarbons such as CH_2Cl_2, $CHCl_3$, $ClCH_2CH_2Cl$ and the like or mixtures thereof. The reaction may be effected in the presence of an acid. The nature of the acid is not critical. Examples of acids used for this reaction includes CH_3COOH, C_2H_5COOH, butyric acid, benzenesulfonic acid, p-toluenesulfonic acid and the like. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar or He. The reaction may be carried out at a temperature in the range of 25 °C to 180 °C, preferably in the range of 25 °C to 60 °C. The reaction is generally instantaneous and the duration of the reaction may range from 0.25 to 12 h, preferably 0.25 to 2 h.--

The last full paragraph on page 33 has been amended as follows:

--The pharmaceutically acceptable salts are prepared by reacting the compound of formula (I) with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases like lysine, arginine, diethanolamine, choline, guanidine and their

derivatives etc. may also be used. Alternatively, acid addition salts are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid, salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, THF, dioxane etc. Mixture of solvents may also be used.--

The fifth full paragraph on page 50 has been amended as follows:

--A mixture of ethyl 2-bromo-3-[4-[2-[2-ethyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy]phenyl]propanoate (1.70 g, 3.89 mmol) (obtained from preparation 24), fused sodium acetate (637 mg, 7.78 mmol) and thiourea (592 mg, 7.78 mmol) in ethanol (10 ml) was refluxed for 12 h. The reaction mixture was cooled to room temperature and the resultant solid was filtered and dried to afford the title compound (1.35 g, 89 %).--

The last full paragraph on page 56 has been amended as follows:

--The title compound (138 mg, 40 %) was prepared from 2-ethyl-4-trifluoromethyl-1,6-dihydro-6-pyrimidone (200 mg, 1.04 mmol) and 4-[2-bromoethoxy]benzaldehyde (238.5 mg, 1.04 mmol) in presence of K_2CO_3 (287.5 mg, 2.08 mmol) as base by a similar procedure to that described in preparation 1.--

The last full paragraph on page 57 has been amended as follows:

--To magnesium turnings (6.6 g, 0.277 mol) in methanol (150 mL) was added a solution of ethyl [4-[[2,4-dioxo-1,3-thiazolidine-5-yl]methylene]phenoxy]acetate (5 g, 16.3 mmol) in methanol (50 mL) and stirred for 12 h, maintaining the temperature below 50 °C, when the reaction initiates as evidenced by hydrogen evolution and heat generation. The reaction mixture

was poured into ice water (150 mL), neutralised with 10 % aqueous hydrochloric acid, and the solution was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with water (150 mL) brine (100 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel in 2 % methanol in dichloromethane to give the title compound (2.3 g, 46 %. mp : 107 °C.--

The first full paragraph on page 59 has been amended as follows:

--To a stirred solution of [4-[[2,4-dioxo-1,3-thiazolidine-5-yl]methyl]phenoxy]acetic acid (1.9 g, 6.75 mmol) in dichloromethane (15 mL) was added triethyl amine (1.876 mL, 1.36 g, 13.48 mmol) followed by pivaloyl chloride (0.913 mL, 899 mg, 5.46 mmol) at 0 °C and was further stirred for 1 h at 0 °C. The reaction mixture was added to a solution of 2-amino-N-methyl benzamide (920 mg, 6.13 mmol) in acetic acid (10 mL) and xylene (10 mL) and the reaction mixture was stirred for 30 min at 25°C. The solvents were removed under reduced pressure and the product was purified to yield the title compound (2.51 g, 91 %). mp = 201-203 °C.--

The last full paragraph on page 67 has been amended as follows:

--The title compound (310 mg, 79 %) was obtained from 4-[[1-methyl-4-oxo-1,4-dihydro-2-quinazolinyl]methoxy]benzaldehyde (294 mg, 1.0 mmol) (obtained from preparation 15) and thiazolidine-2,4-dione (117 mg, 1.0 mmol) by a similar procedure to that described in example 1.--

The first full paragraph on page 74 has been amended as follows:

--To a stirred solution of [4-[[2,4-dioxo-1,3-thiazolidine-5-y1]methyl]phenoxy]acetic acid (1.9 g, 6.75 mmol) in dichloromethane (15 mL) was added triethyl amine (1.876 mL, 1.36 g, 13.48 mmol) followed by pivaloyl chloride (0.913 mL, 899 mg, 5.46 mmol) at 0 °C and

stirring was continued for 1 h at 0 °C. The above reaction mixture was added to a solution of 2-amino-Nmethyl benzamide (920 mg, 6.13 mmol) in xylene (20 mL) containing pTsOH.H_2O (646 mg, 3.4 mmol) and refluxed for 24 h. The reaction mixture was cooled to room temperature and xylene was removed under reduced pressure. Water (50 mL) was added to the residue and extracted with $CHCl_3$ (3 x 25 mL). The combined $CHCl_3$ extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to yield the title compound (1.79 g, 58 %).--

The fourth full paragraph on page 84 has been amended as follows:

--5-[4-[2-[2-Ethyl-4-trifluoromethyl-6-oxo-1,6-dihydro-l-pyrimidinyl]ethoxy]phenyl methylene]thiazolidine-2,4-dione :--

The first full paragraph after the structure in Example 35 on page 85 has been amended as follows:

--The title compound (0.3 g, 66 %) was obtained from 5-[4-[2-[2-ethyl-4-trifluoromethyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy]phenyl methylene]thiazolidine-2,4-dione (0.45 g, 1.025 mmol) obtained from example 34 by a similar procedure to that described in example 17.mp : 135 °C.--

The first full paragraph on page 86 has been amended as follows:

--The title compound (1.6 g, 89 %) was obtained from 5-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl methyl]-2-iminothiazolidine-4-one (1.8g, 4.4 mmol) (obtained from preparation 35) by a similar procedure to that described in example 19 (method B), 242-244 °C.--

The fifth full paragraph on page 88 has been amended as follows:

--The title compound (140 mg, 64 %) was obtained from 5-[4-[[6,7-dimethoxy-3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl methyl]thiazolidine-2,4-dione (210 mg, 0.46 mmol) (obtained from example 39) by a similar procedure to that described in example 28. mp : 275 °C.--

The second full paragraph on page 89 has been amended as follows:

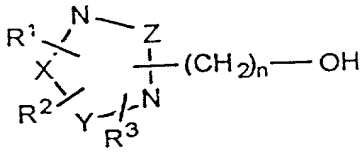
--To a stirred solution of 5-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl methyl]thiazolidine-2,4-dione (10.0 g, 25.3 mmol) (obtained from example 22) in methanol (100 mL) was added a solution of t-BuOK (3.40 g, 30.3 mmol) in methanol (50 mL) dropwise at 30 °C. During this period the suspension slowly dissolved completely and a white solid precipitated out which was stirred further for 1h. The solid was filtered and washed with methanol (20 mL) and dried to afford the title compound (9.8 g, 90 %). mp : 302 °C.--

IN THE CLAIMS :

Please cancel claims 1-25.

Please add the following new claims 26 and 27.

26. A compound of formula (VI)

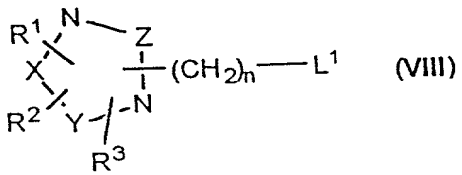


(VI)

its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts or its pharmaceutically acceptable solvates where one of X, Y or Z represent C=O or C=S and one of the remaining of X, Y and Z represent C=and the other of the remaining X, Y and Z

represents C=C; R^1, R^2 and R^3 are substituents either on X, Y or Z or on a nitrogen atom and may be the same or different and represents hydrogen, halogen, hydroxy or nitro, or optionally substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, acyl, acyloxy, hydroxyalkyl, amino, acylamino, arylamino, aminoalkyl, aryloxy, alkoxycarbonyl, alkylamino, alkoxyalkyl, thioalkyl, alkylthio or carboxylic acid or its derivatives or sulfonic acid or its derivatives, with the provision that when R^1, R^2 or R^3 is on a nitrogen atom it does not represent hydrogen, halogen, nitro, carboxy or sulfonic acid groups; or any two of R^1, R^2 and R^3 along with the adjacent atoms to which they are attached may form a substituted or unsubstituted cyclic structure of 4 to 7 atoms with one or more double bonds which may be carbocyclic or may contain one or more heteroatoms selected from oxygen, nitrogen and sulfur; the linking group represented by $(CH_2)_n$-O- may be attached either through nitrogen atom or through X, Y or Z where n is an integer ranging from 1-4.

27. A compound of formula (VIII)



(VIII)

its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts or its pharmaceutically acceptable solvates where one of X, Y or Z represent C=O or C=S and one of the remaining of X, Y and Z represent C=and the other of the remaining X, Y and Z represents C=C; R^1, R^2 and R^3 are substituents either on X, Y or Z or on a nitrogen atom and may be the same or different and represents hydrogen, halogen, hydroxy or nitro, or optionally substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl,

aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, acyl, acyloxy, hydroxyalkyl, amino, acylamino, arylamino, aminoalkyl, aryloxy, alkoxycarbonyl, alkylamino, alkoxyalkyl, thioalkyl, alkylthio or carboxylic acid or its derivatives or sulfonic acid or its derivatives, with the provision that when R^1, R^2 or R^3 is on a nitrogen atom it does not represent hydrogen, halogen, nitro, carboxy or sulfonic acid groups; or any two of R^1, R^2 and R^3 along with the adjacent atoms to which they are attached may form a substituted or unsubstituted cyclic structure of 4 to 7 atoms with one or more double bonds which may be carbocyclic or may contain one or more heteroatoms selected from oxygen, nitrogen and sulfur; the linking group represented by $(CH_2)_n$-O- may be attached either through nitrogen atom or through X, Y or Z where n is an integer ranging from 1-4; and L^1 represents a halogen atom or a leaving group.

<u>Remarks</u>

The amendments to the specification are:

Page 10, line 18 a "," after "$NHCOOCH_2C_6H_5$" was replaced with a ";";

Page 28, line 11, a "." was inserted after "conditions";

Page 32, line 20, a "," was inserted after "DMSO";

Page 33, line 27, a "," was inserted after "maleic acid";

Page 50, line 15, "propaneate" was replaced with "propanoate";

Page 56, line 16, "2-ethyl-4-trifluoromethyl-(1,6-" was replaced with "2-ethyl-4-trifluoromethyl-1,6-";

Page 57, line 18, "iced" was replaced with "ice";

Page 59, line 3, "furthe" was replaced with "further";

Page 67, last line, "□" was deleted;

Page 74, line 5, "triethy lamine" was replaced with "triethyl amine";

Page 84, line 11, "methyl" was replaced with "methylene".

Page 85, line 9 (second line after structure in Example 35), "methyl" was replaced with "methylene";

Support for the amendment on page 84, line 11 and page 85, lines 1-3 after the structure in Example 35 is found in the structure in Example 34.

Page 86, line 4, "2444" was replaced with "244";

Page 88, line 11, "5-[4-[[(6,7-" was replaced with "5-[4-[[6,7-";

Page 89, line 6, "tBuOK" was replaced with "t-BuOK".

Respectfully submitted,

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The first full paragraph on page 10 has been amended as follows:

--When R^1, R^2 and R^3 groups are attached to X, Y, and Z it is preferred that R^1, R^2, and R^3 are selected from hydrogen, halogen atom such as fluorine, chlorine, bromine, or iodine; hydroxy, nitro; substituted or unsubstituted (C_1-C_{12})alkyl group, especially, linear or branched (C_1-C_6)alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, t-butyl and the like; cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like; cycloalkyloxy group such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and the like; aryl group such as phenyl or naphthyl, the aryl group may be substituted; aralkyl such as benzyl or phenethyl, the aralkyl group may be substituted; heteroaryl group such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, oxadiazolyl, tetrazolyl, benzopyranyl, benzofuranyl and the like, the heteroaryl group may be substituted; heterocyclyl groups such as aziridinyl, pyrrolidinyl, morpholinyl, piperidinyl and the like, the heterocyclyl group may be substituted; aryloxy such as phenoxy, naphthyloxy, the aryloxy group may be substituted; alkoxycarbonyl such as methoxycarbonyl or ethoxycarbonyl; aryloxycarbonyl group such as optionally substituted phenoxycarbonyl; arylamino group such as HNC_6H_5; amino group; amino(C_1-C_6)alkyl; hydroxy(C_1-C_6)alkyl; (C_1-C_6)alkoxy; thio(C_1-C_6)alkyl; (C_1-C_6)alkylthio; acyl group such as acetyl, propionyl or benzoyl, the acyl group may be substituted; acylamino groups such as $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_6H_5$, aralkoxycarbonylamino group such as $NHCOOCH_2C_6H_5$[,]; alkoxycarbonylamino group such as $NHCOOC_2H_5$, $NHCOOCH_3$ and the like; carboxylic acid or its derivatives such as amides, like $CONH_2$, CONHMe, $CONMe_2$, CONHEt, $CONEt_2$, CONHPh and the like, the carboxylic acid derivatives may be substituted; acyloxy group such as OCOMe, OCOEt, OCOPh and the like which may optionally be substituted; sulfonic acid or its derivatives such as SO_2NH_2, SO_2NHMe, SO_2NMe_2, SO_2NHCF_3 and the like; the

sulfonic acid derivatives may be substituted.--

The first full paragraph on page 28 has been amended as follows:

--The process described in the above embodiment is novel and unique since the heterocycle has been built in the final step of the process. In the present process no side products are observed. The yields are high and no purification is required for any intermediate involved. The process described in the above embodiment does not involve any stringent conditions. This process works well for both small scale and large scale reactions. The process described in the above embodiment is preferably used for compounds of formula (I) wherein R^2 and R^3 together form a cyclic structure as defined earlier with Y, wherein Y represents C=C.--

The last full paragraph on page 32 has been amended as follows:

--The reaction of compound of the formula (XXIV) with a compound of formula (XXV) to yield a compound of the formula (XXVI) may be carried out neat or in presence of solvent such as xylene, toluene, dioxane, DMF, $DMSO_2$ halogenated hydrocarbons such as CH_2Cl_2, $CHCl_3$, $ClCH_2CH_2Cl$ and the like or mixtures thereof. The reaction may be effected in the presence of an acid. The nature of the acid is not critical. Examples of acids used for this reaction includes CH_3COOH, C_2H_5COOH, butyric acid, benzenesulfonic acid, p-toluenesulfonic acid and the like. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar or He. The reaction may be carried out at a temperature in the range of 25 °C to 180 °C, preferably in the range of 25 °C to 60 °C The reaction is generally instantaneous and the duration of the reaction may range from 0.25 to 12 h, preferably 0.25 to 2 h.--

The last full paragraph on page 33 has been amended as follows:

--The pharmaceutically acceptable salts are prepared by reacting the compound of formula (I) with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases like lysine, arginine, diethanolamine, choline, guanidine and their derivatives etc. may also be used. Alternatively, acid addition salts are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid, salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, THF, dioxane etc. Mixture of solvents may also be used.--

The fifth full paragraph on page 50 has been amended as follows:

--A mixture of ethyl 2-bromo-3-[4-[2-[2-ethyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy]phenyl][propaneate]propanoate (1.70 g, 3.89 mmol) (obtained from preparation 24), fused sodium acetate (637 mg, 7.78 mmol) and thiourea (592 mg, 7.78 mmol) in ethanol (10 ml) was refluxed for 12 h. The reaction mixture was cooled to room temperature and the resultant solid was filtered and dried to afford the title compound (1.35 g, 89 %).--

The last full paragraph on page 56 has been amended as follows:

--The title compound (138 mg, 40 %) was prepared from 2-ethyl-4-trifluoromethyl-[(]1,6-dihydro-6-pyrimidone (200 mg, 1.04 mmol) and 4-[2-bromoethoxy]benzaldehyde

(238.5 mg, 1.04 mmol) in presence of K_2CO_3 (287.5 mg, 2.08 mmol) as base by a similar procedure to that described in preparation 1.--

The last full paragraph on page 57 has been amended as follows:

--To magnesium turnings (6.6 g, 0.277 mol) in methanol (150 mL) was added a solution of ethyl [4-[[2,4-dioxo-1,3-thiazolidine-5-yl]methylene]phenoxy]acetate (5 g, 16.3 mmol) in methanol (50 mL) and stirred for 12 h, maintaining the temperature below 50 °C, when the reaction initiates as evidenced by hydrogen evolution and heat generation. The reaction mixture was poured into ice [iced] water (150 mL), neutralised with 10 % aqueous hydrochloric acid, and the solution was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with water (150 mL) brine (100 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel in 2 % methanol in dichloromethane to give the title compound (2.3 g, 46 %. mp : 107 °C.--

The first full paragraph on page 59 has been amended as follows:

--To a stirred solution of [4-[[2,4-dioxo-1,3-thiazolidine-5-yl]methyl]phenoxy]acetic acid (1.9 g, 6.75 mmol) in dichloromethane (15 mL) was added triethyl amine (1.876 mL, 1.36 g, 13.48 mmol) followed by pivaloyl chloride (0.913 mL, 899 mg, 5.46 mmol) at 0 °C and was [furthe] further stirred for 1 h at 0 °C. The reaction mixture was added to a solution of 2-amino-N-methyl benzamide (920 mg, 6.13 mmol) in acetic acid (10 mL) and xylene (10 mL) and the reaction mixture was stirred for 30 min at 25°C. The solvents were removed under reduced pressure and the product was purified to yield the title compound (2.51 g, 91 %). mp = 201-203 °C.--

The last full paragraph on page 67 has been amended as follows:

--The title compound (310 mg, 79 %) was obtained from 4-[[1-methyl-4-oxo-1,4-dihydro-2-quinazolinyl]methoxy]benzaldehyde (294 mg, 1.0 mmol) (obtained from preparation 15) and thiazolidine-2,4-dione (117 mg, 1.0 mmol) by a similar procedure to that described in example 1.[□]--

The first full paragraph on page 74 has been amended as follows:

--To a stirred solution of [4-[[2,4-dioxo-1,3-thiazolidine-5-y1]methyl]phenoxy]acetic acid (1.9 g, 6.75 mmol) in dichloromethane (15 mL) was added triethyl amine [triethy lamine] (1.876 mL, 1.36 g, 13.48 mmol) followed by pivaloyl chloride (0.913 mL, 899 mg, 5.46 mmol) at 0 °C and stirring was continued for 1 h at 0 °C. The above reaction mixture was added to a solution of 2-amino-Nmethyl benzamide (920 mg, 6.13 mmol) in xylene (20 mL) containing pTsOH.H_2O (646 mg, 3.4 mmol) and refluxed for 24 h. The reaction mixture was cooled to room temperature and xylene was removed under reduced pressure. Water (50 mL) was added to the residue and extracted with $CHCl_3$ (3 x 25 mL). The combined $CHCl_3$ extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to yield the title compound (1.79 g, 58 %).--

The fourth full paragraph on page 84 has been amended as follows:

--5-[4-[2-[2-Ethyl-4-trifluoromethyl-6-oxo-1,6-dihydro-l-pyrimidinyl]ethoxy]phenyl methylene [methyl]]thiazolidine-2,4-dione :--

The first full paragraph after the structure in Example 35 on page 85 has been amended as follows:

--The title compound (0.3 g, 66 %) was obtained from 5-[4-[2-[2-ethyl-4-

trifluoromethyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy]phenyl [methyl]methylene]thiazolidine-2,4-dione (0.45 g, 1.025 mmol) obtained from example 34 by a similar procedure to that described in example 17.mp : 135 °C.--

The first full paragraph on page 86 has been amended as follows:

--The title compound (1.6 g, 89 %) was obtained from 5-[4-[2-[2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl]ethoxy]phenyl methyl]-2-iminothiazolidine-4-one (1.8g, 4.4 mmol) (obtained from preparation 35) by a similar procedure to that described in example 19 (method B), 242-244[4] °C.--

The fifth full paragraph on page 88 has been amended as follows:

--The title compound (140 mg, 64 %) was obtained from 5-[4-[[[(]6,7-dimethoxy-3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl methyl]thiazolidine-2,4-dione (210 mg, 0.46 mmol) (obtained from example 39) by a similar procedure to that described in example 28. mp : 275 °C.--

The second full paragraph on page 89 has been amended as follows:

--To a stirred solution of 5-[4-[[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl] methoxy]phenyl methyl]thiazolidine-2,4-dione (10.0 g, 25.3 mmol) (obtained from example 22) in methanol (100 mL) was added a solution of t-BuOK (3.40 g, 30.3 mmol) in methanol (50 mL) dropwise at 30 °C. During this period the suspension slowly dissolved completely and a white solid precipitated out which was stirred further for 1h. The solid was filtered and washed with methanol (20 mL) and dried to afford the title compound (9.8 g, 90 %). mp : 302 °C.--